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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,106	12/21/2001	Zaoyuan Peng	433112000700	5878

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,106	PENG ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *29-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/29/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I(claims 1-28) without traverse in their response received 7/12/2004 is acknowledged. Claims 1-28 are herein examined.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/29/2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-14, 17-21, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Gould-Rothberg(US Patent 6,620,615).

With regard to claim 1, Gould-Rothberg teach a method for identifying a gene whose expression level is associated with a disease state(i.e. tuberous sclerosis see Abstract, Col. 1 lines

30-45), the method comprising: identifying at least one gene having a nucleic acid sequence encoding a protein comprising a physical characteristic(column 1 for example several GPCR genes, specifically named TSC1-41 and the physical characteristic of the seven transmembrane domain Col. 1 line 20); selecting a polynucleotide sequence from the nucleic acid sequence(Col. 1 lines 39-45 specifically TSC7 encoding a G-protein coupled receptor), wherein the polynucleotide sequence is specific for a protein comprising the physical characteristic(Abstract and Column 1 as cited above for example, physical characteristic of a G-protein coupled receptor and in Column 1 line 20 a seven transmembrane domain structure); detecting a level of expression of the polynucleotide sequence or a complement thereof in a diseased tissue sample(Col. 57 lines 11-34); detecting a level of expression of the polynucleotide sequence or a complement thereof in a normal tissue sample(Col. 78 lines 21-31 the reference teaches the expression level of one or more of the TSCX sequences in a test and reference cell population) ; and comparing the level of expression of the polynucleotide sequence or a complement in the diseased tissue sample to a level of expression of the gene in the control tissue sample(Col 78 lines 66-67 bridging into Col. 79, lines 1-8) wherein an altered level of expression of the polynucleotide sequence or a complement in the diseased tissue sample correlates with the disease state(Col. 79 lines 32-67 bridging to Col. 80 lines 1-61). Specifically, the reference teaches novel nucleic acids, polypeptides encoded by the novel nucleic acids, and methods of using these sequences. In one aspect, the invention provides a nucleic acid encoding a novel G-protein coupled receptor that was discovered through changes in expression patterns of multiple nucleic acid sequences in human fibroblast cells derived from individuals with the TSC-associated conditions ashleaf spots, shagreen patches and

ungula fibromas(Col.4 lines 5-14). 41 single copy nucleic acid sequences whose expression levels differed in TSC tissue and normal tissue were chosen for further characterization (i.e. TSC:1-41), with a TSC7 nucleic acid according to the invention being able to encode a novel G-protein coupled receptor and also consisting of the physical characteristics associated with a G-Protein Coupled Receptor(GPCR)(Col. 4 lines 32-36).

With regard to claims 2, 3, 5, 8, and 9, the reference teaches the method of claim 1, wherein the physical characteristic comprises seven transmembrane (7-TM) domains in their TSC7(SEQ ID NO:1) novel G-protein coupled receptor that is "characterized by a seven transmembrane motif, and are involved in regulation of a variety of cell processes such as proliferation, migration, adhesion, and possibly cellular transformation.

With regard to claim 4, the reference teaches the method of claim 1, wherein the physical characteristic comprises an amino acid sequence comprising an Asp-Arg-Tyr (DRY) motif in their TSC7, SEQ ID NO:1 at residues 136-138.

With regard to claims 6 and 7, the reference teaches the method of claim 1 wherein the physical characteristic comprises a signal peptide sequence characteristic of a secreted protein and/or mitochondria in its teaching of TSC34(Accession # D13665) which contains a putative signal peptide using neural networks and hidden Markov models trained on eukaryotes with a cleavage site between positions 21 and 22(See attached SIGNAL-P 3.0 prediction results).

With regard to claims 10, 11, and 12 Gould-Rothberg teach the method of claim 1, wherein the identification of the gene comprises searching a nucleic acid sequence database that is an electronic library and uses a search algorithm for nucleic acid sequences which encode a protein comprising the physical characteristic. Specifically, Gould-Rothberg teach the use of

GENECALLING™ expression analysis for the identification of genes whose transcript levels varied between normal and lesion samples(Col. 4 lines 20-24)(see also attached description of GENECALLING™).

With regard to claim 13, Gould-Rothberg teach the method of claim 1, wherein the identification of the gene comprises selecting at least one gene whose expression is known to correlate with a disease state specifically in their teaching of Col. 3 lines 12-25 of diagnosing hyperproliferative disorders in a subject through measuring the expression of one or more nucleic acid sequences selected from the group consisting of TSCs 1-41.

With regard to claims 14, Gould-Rothberg teach the method of claim 1, wherein the detection of the level of expression of the polynucleotide sequence comprises: selecting at least one isolated oligonucleotide comprising the polynucleotide sequence or a fragment thereof; contacting the oligonucleotide with a nucleic acid preparation from the tissue sample; and detecting a level of expression of the polynucleotide sequence by detecting an amount of hybridization of the nucleic acid preparation to the oligonucleotide under stringent conditions. Specifically, Gould-Rothberg teach a method that can be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant TSC-X expression or activity(Col. 57 lines 11-35). Furthermore, it is taught in Col. 27 lines 25-36, that "probes based on the human TSC-X nucleotide sequence can be used to detect transcripts or genomic sequences encoding the same or homologous proteins" and also that "such probes can be used as a part of a diagnostic kit for identifying cells or tissues which misexpress a TSC-X protein such as by measuring a level of a TSC-X encoding nucleic acid in a sample of cells from a subject e.g., detecting TSC-X mRNA levels". It is additionally taught in Col. 27 that "the oligonucleotide

typically comprises a region of nucleotide sequence that hybridizes under stringent conditions"(lines 19-20).

With respect to claim 17, Gould-Rothberg teach that an oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 25, etc(Col. 27 lines 18-20) thus teaching that the selection of polynucleotide sequence determines an efficiency of hybridization to a complementary sequence.

With respect to claims 18 and 19, Gould-Rothberg teach in Col. 27 lines 27-31 that the probes further comprise a label group that can be a fluorescent compound to be used for measuring the level of an TSC-X encoding nucleic acid in a sample of cells from a subject e.g., detecting TSC-X mRNA levels(Col. 27 Line 35).

With respect to claims 20 and 21, Gould-Rothberg teach in Col. 60 lines 40-45, that oligonucleotides are hybridized to PCR amplified target DNA.

With respect to claim 23, Gould-Rothberg teach the method of claim 1, wherein comparing the level of expression of the gene comprises: providing at least one isolated oligonucleotide comprising the polynucleotide sequence or a fragment thereof; contacting the oligonucleotide with an amount of nucleic acid preparation from a disease tissue sample (hyperproliferative disorder Col. 79 lines 35-55); contacting the oligonucleotide with an equal amount of nucleic acid preparation from a normal tissue sample; and comparing the level of expression of the polynucleotide sequence in the tissue samples by detecting an amount of hybridization of each nucleic acid preparation to the oligonucleotide under stringent conditions. Specifically, the reference teaches the method of claim 1, wherein the "expression of sequences in test and control("normal") populations of cells can be compared using any art-recognized

method for comparing expression of nucleic acid sequences"(Col. 79-82 specifically from lines 1-8 Col. 79).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 15, 16, and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gould-Rothberg(US Patent 6,620,615) in view of Schena et al(Science Vol. 270, 1995).

With regard to claim 1, Gould-Rothberg teach a method for identifying a gene whose expression level is associated with a disease state(i.e. tuberous sclerosis see Abstract, Col. 1 lines 30-45), the method comprising: identifying at least one gene having a nucleic acid sequence encoding a protein comprising a physical characteristic(column 1 for example several GPCR genes, specifically named TSC1-41 and the physical characteristic of the seven transmembrane domain Col. 1 line 20); selecting a polynucleotide sequence from the nucleic acid sequence(Col. 1 lines 39-45 specifically TSC7 encoding a G-protein coupled receptor), wherein the polynucleotide sequence is specific for a protein comprising the physical characteristic(Abstract and Column 1 as cited above for example, physical characteristic of a G-protein coupled receptor and in Column 1 line 20 a seven transmembrane domain structure); detecting a level of expression of the polynucleotide sequence or a complement thereof in a diseased tissue sample(Col. 57 lines 11-34); detecting a level of

expression of the polynucleotide sequence or a complement thereof in a normal tissue sample(Col. 78 lines 21-31 the reference teaches the expression level of one or more of the TSCX sequences in a test and reference cell population) ; and comparing the level of expression of the polynucleotide sequence or a complement in the diseased tissue sample to a level of expression of the gene in the control tissue sample(Col 78 lines 66-67 bridging into Col. 79, lines 1-8) wherein an altered level of expression of the polynucleotide sequence or a complement in the diseased tissue sample correlates with the disease state(Col. 79 lines 32-67 bridging to Col. 80 lines 1-61). Specifically, the reference teaches novel nucleic acids, polypeptides encoded by the novel nucleic acids, and methods of using these sequences. In one aspect, the invention provides a nucleic acid encoding a novel G-protein coupled receptor that was discovered through changes in expression patterns of multiple nucleic acid sequences in human fibroblast cells derived from individuals with the TSC-associated conditions ashleaf spots, shagreen patches and ungula fibromas(Col.4 lines 5-14). 41 single copy nucleic acid sequences whose expression levels differed in TSC tissue and normal tissue were chosen for further characterization (i.e. TSC:1-41), with a TSC7 nucleic acid according to the invention being able to encode a novel G-protein coupled receptor and also consisting of the physical characteristics associated with a G-Protein Coupled Receptor(GPCR)(Col. 4 lines 32-36).

With regard to claims 2, 3, 5, 8, and 9, the reference teaches the method of claim 1, wherein the physical characteristic comprises seven transmembrane (7-TM) domains in their TSC7(SEQ ID NO:1) novel G-protein coupled receptor that is "characterized by a seven transmembrane motif, and are involved in regulation of a variety of cell processes such as proliferation, migration, adhesion, and possibly cellular transformation.

With regard to claim 4, the reference teaches the method of claim 1, wherein the physical characteristic comprises an amino acid sequence comprising an Asp-Arg-Tyr (DRY) motif in their TSC7, SEQ ID NO:1 at residues 136-138.

With regard to claims 6 and 7, the reference teaches the method of claim 1 wherein the physical characteristic comprises a signal peptide sequence characteristic of a secreted protein and/or mitochondria in its teaching of TSC34 which contains a putative signal peptide using neural networks and hidden Markov models trained on eukaryotes with a cleavage site between positions 21 and 22(See attached SIGNAL-P 3.0 prediction results).

With regard to claims 10, 11, and 12 Gould-Rothberg teach the method of claim 1, wherein the identification of the gene comprises searching a nucleic acid sequence database that is an electronic library and uses a search algorithm for nucleic acid sequences which encode a protein comprising the physical characteristic. Specifically, Gould-Rothberg teach the use of GENECALLING^{TM} expression analysis for the identification of genes whose transcript levels varied between normal and lesion samples(Col. 4 lines 20-24)(see also attached description of GENECALLING^{TM}).

With regard to claim 13, Gould-Rothberg teach the method of claim 1, wherein the identification of the gene comprises selecting at least one gene whose expression is known to correlate with a disease state specifically in their teaching of Col. 3 lines 12-25 of diagnosing hyperproliferative disorders in a subject through measuring the expression of one or more nucleic acid sequences selected from the group consisting of TSCs 1-41.

With regard to claims 14, Gould-Rothberg teach the method of claim 1, wherein the detection of the level of expression of the polynucleotide sequence comprises: selecting at least

one isolated oligonucleotide comprising the polynucleotide sequence or a fragment thereof; contacting the oligonucleotide with a nucleic acid preparation from the tissue sample; and detecting a level of expression of the polynucleotide sequence by detecting an amount of hybridization of the nucleic acid preparation to the oligonucleotide under stringent conditions. Specifically, Gould-Rothberg teach a method that can be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant TSC-X expression or activity(Col. 57 lines 11-35). Furthermore, it is taught in Col. 27 lines 25-36, that "probes based on the human TSC-X nucleotide sequence can be used to detect transcripts or genomic sequences encoding the same or homologous proteins" and also that "such probes can be used as a part of a diagnostic kit for identifying cells or tissues which misexpress a TSC-X protein such as by measuring a level of a TSC-X encoding nucleic acid in a sample of cells from a subject e.g., detecting TSC-X mRNA levels". It is additionally taught in Col. 27 that "the oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions"(lines 19-20).

With regard to claims 15 and 16 teaches the method of claim 14 wherein the oligonucleotide is attached to a solid support that is a microarray. Specifically, Gould-Rothberg teach that mutations in TSC-X can be identified by hybridizing a sample and control nucleic acids e.g., DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotide probes on the microscopic level.(Col. 58 lines 60-66).

With respect to claim 17, Gould-Rothberg teach that an oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least

about 12, 25, etc(Col. 27 lines 18-20) thus teaching that the selection of polynucleotide sequence determines an efficiency of hybridization to a complementary sequence.

With respect to claims 18 and 19, Gould-Rothberg teach in Col. 27 lines 27-31 that the probes further comprise a label group that can be a fluorescent compound to be used for measuring the level of an TSC-X encoding nucleic acid in a sample of cells from a subject e.g., detecting TSC-X mRNA levels(Col. 27 Line 35).

With respect to claims 20 and 21, Gould-Rothberg teach in Col. 60 lines 40-45, that oligonucleotides are hybridized to PCR amplified target DNA.

With respect to claim 23, Gould-Rothberg teach the method of claim 1, wherein comparing the level of expression of the gene comprises: providing at least one isolated oligonucleotide comprising the polynucleotide sequence or a fragment thereof; contacting the oligonucleotide with an amount of nucleic acid preparation from a disease tissue sample (hyperproliferative disorder Col. 79 lines 35-55); contacting the oligonucleotide with an equal amount of nucleic acid preparation from a normal tissue sample; and comparing the level of expression of the polynucleotide sequence in the tissue samples by detecting an amount of hybridization of each nucleic acid preparation to the oligonucleotide under stringent conditions. Specifically, the reference teaches the method of claim 1, wherein the "expression of sequences in test and control("normal") populations of cells can be compared using any art-recognized method for comparing expression of nucleic acid sequences"(Col. 79-82 specifically from lines 1-8 Col. 79).

Gould-Rothberg do not teach the above method wherein the oligonucleotides are attached to a solid support that is a microarray for the purpose of detecting the level of expression of the TSC-X polynucleotide sequences.

However, with regard to claims 15, 16, and 24-28 Schena et al. teach quantitative monitoring of gene expression patterns with a complementary DNA microarray wherein "fluorescent probes were prepared from total Arabidopsis mRNA by a single round of reverse transcription"(Pg. 467) and the fluorescent probes were prepared "from two mRNA sources with the use of reverse transcriptase in the presence of fluorescein- and lissamine-labeled nucleotide analogs"(Pg. 468). Lastly the reference teaches that the "resulting fluorescently labeled cDNA mixture was hybridized to an array at high stringency and scanned with a laser"(Bridging pages 467-468).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Gould-Rothberg which teaches the use of a high density array for mutation detection and that "expression of sequences in test and control("normal") populations of cells can be compared using any art-recognized method for comparing expression of nucleic acid sequences"(Col. 79-82 specifically from lines 1-8 Col. 79) in view of Schena et al. who teach one art recognized method for comparing expression in their use of a microarray for expression detection as the system represents an expected benefit of providing a "high-capacity system developed to monitor the expression of many genes in parallel".

3. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gould-Rothberg(US Patent 6,620,615) in view of Boom et al.(Journal of Clinical Microbiology, May 1999, p. 1489-1497).

While the teachings of Gould-Rothberg can be seen above, the reference does not teach the method wherein the nucleic acid preparation from the tissue sample is amplified using QPCR.

However, with regard to claim 22, Boom et al. teach a highly sensitive assay for detection and quantitation of human cytomegalovirus DNA in serum and plasma by PCR and electrochemiluminescence and furthermore a quantitative PCR assay (Q-PCR) for the detection of human cytomegalovirus (CMV) in plasma and serum. The reference further teaches that "the Q-PCR assay is quantitative in the range of 100 to 150,000 copies of CMV/ml, independent of anticoagulant.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Gould-Rothberg with that of Boom et al. for the expected benefit taught by Boom et al. of using Q-PCR that "will reliably detect fourfold differences in viral load" which would make the method of Gould-Rothberg a more discernable detection method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris

9/29/2004

JEFFREY FREDMAN
PRIMARY EXAMINER
9/29/04